

**REMARKS**

Claims 1-4, 10-22, and 23-25 were pending. Claim 1 has been amended to make explicit that the protein is isolated (see, e.g., page 21, lines 26-29) and that positions corresponding to Ser-63 and Arg-192 of SEQ ID NO:7 or SEQ ID NO:8 is replaced with another amino acid (see, e.g., page 8, lines 20-21). Claim 11 has been amended to correct an inadvertent typographical error.

Thus, claims 1-4, 10-22, and 23-25 are pending as shown above. Claims 10-18 and 24 are withdrawn as being drawn to non-elected inventions and claims 1-4, 19-23, and 25 are under active consideration.

**Restriction Requirement**

Applicants affirm the election with traverse of Group I, which corresponds to claims 1-4 and 15-25, drawn to immunogenic detoxified LT or CT proteins, and the further election of species, also with traverse, of an *E. coli* heat labile toxin subunit A with a substitution of Asn or Gly (Group 3).

**Rejoinder**

Applicants request that claims 10-14, drawn to a method of using the immunogenic detoxified LT or CT proteins of Group I be rejoined per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants request that claims 10-14 be rejoined and examined upon allowance of any of the claims of Group I.

In addition, the Examiner is reminded that claims 15-18 and 24 were withdrawn because of an election of species requirement rather than a restriction requirement (see paper of September 26, 2006), and should be examined upon allowance of generic claim 1 per 37 C.F.R. § 1.141, which sets forth the rules, upon allowance of any generic claim, all claimed species should be examined in claims written in dependent form or that otherwise include all the limitations of the generic claim.

**Priority**

Applicants submit that the priority information, as amended, complies with 35 U.S.C. § 120.

**35 U.S.C. § 112, second paragraph**

Claims 1-4, 19-23, and 25 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being “indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” (Office Action, page 5).

(a) The Office Action alleges that claims 1-4, 19-23, and 25 are “incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections” (Office Action, page 5). In particular, the Office Action alleges that all of the claims recite the phrase “the amino acid at, or in positions corresponding to” and that “[w]hile it is clear that the amino acid at position Ser-63 and Arg-192 are to be replaced, the instant Specification has not provided a definition for determining what a *corresponding position* is, nor provides a structural cooperative relationship to be able to ascertain what or where a corresponding position is” (Office Action, page 6).

Applicants respectfully traverse the rejection.

The definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular disclosure at issue, (2) the teachings of the art, and (3) the interpretation that would be given by one possessing an ordinary level of skill in the pertinent art at the time the invention was made. *See, e.g., In re Marosi*, 218 USPQ 289 (Fed. Cir. 1983). Consequently, a claim that is understandable to one of skill in the art meets the requirements of the second paragraph of 35 U.S.C. § 112.

Applicants submit that the meaning of the phrases “the amino acid at the position corresponding to Ser-63 of SEQ ID NO:7 or SEQ ID NO:8” or “the amino acid at the position corresponding to Arg-192 of SEQ ID NO:7 or SEQ ID NO:8” are clear in the context of the claim. One of skill in the art would understand that the residues that are to be replaced are determined relative to particular reference sequences, that is, SEQ ID

NO:7 or SEQ ID NO:8. Methods of aligning sequences to determine the corresponding positions in related sequences were well known in the art at the time the instant application was filed. Moreover, alignments of LT and CT sequences are shown in Figure 8 of the specification and in Domenighini et al. (see Figure 1), cited at page 7 of the specification. These alignments further demonstrate how to align any given LT or CT sequence to determine which residues correspond to positions 63 and 192 of SEQ ID NO:7 or SEQ ID NO:8.

Claims must be examined on the basis of whether one having ordinary skill in the art would be able to determine the scope of the claim and, if a rejection is made, reasons must be provided why the claim is indefinite. Applicants submit that the Examiner has not provided any reasons or evidence why the cited phrase is indefinite and/or why one having ordinary skill in the art could not determine the scope of the claims. Therefore, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

(b) In addition, claims 1-4, 19-23, and 25 recite an immunogenic detoxified protein comprising mutations that allegedly may read on naturally occurring mutants. Claim 1 has been amended to recite an isolated immunogenic detoxified protein, as suggested by the Examiner. Therefore, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

### **Objection to the Claims**

Claims 1-4, 19-23, and 25 are objected to for containing non-elected subject matter. The Examiner is reminded that claims 1-4, 19-23, and 25 were subjected to an election of species requirement rather than a restriction requirement (see paper of September 26, 2006). Applicants submit that generic claim 1, as currently amended, contains allowable subject matter, and the removal of non-elected species at this time is therefore premature.

In addition, claim 19 is objected to for being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully disagree. Claim 1, from which claim 19 is dependent, recites an isolated immunogenic

detoxified protein comprising the amino acid sequence of subunit A of a cholera toxin (CT-A) or the amino acid sequence of subunit A of an *Escherichia coli* heat labile toxin (LT-A). Claim 19 further limits claim 1 to an immunogenic detoxified protein comprising the amino acid sequence of subunit A of an *Escherichia coli* heat labile toxin (LT-A). Therefore, claim 19 is properly dependent, and withdrawal of the objection to the claim is respectfully requested.

**35 U.S.C. § 102**

Claims 1-4, 19-21, 23, and 25 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the reference of Domenighini et al. (International Patent Application WO 93/13202; hereinafter “Domenighini”) in view of evidence provided by Pizza et al. (Mol. Microbiol. (1994) 14:51-60). In particular, the Office Action alleges that Domenighini discloses an immunogenic detoxified protein comprising the amino acid sequence of subunit A of an *Escherichia coli* heat labile toxin (LT-A) having the mutations Ser63Lys and Arg192Asn and a vaccine composition comprising this protein (Office Action, page 7). The Office Action further alleges that Domenighini inherently anticipates the instantly claimed invention in light of evidence provided by Pizza (1994) showing that Lys63 causes loss of toxicity (see Table 1 and 2) and the Arg192Asn substitution decreases the rate of proteolysis and activation *in vivo* (Office Action, page 7). Applicants respectfully traverse the rejection.

For a reference to anticipate claimed subject matter under 35 U.S.C. § 102, “the reference must teach every aspect of the claimed invention either explicitly or implicitly.” M.P.E.P. § 706.02. Applicants respectfully submit that Domenighini does not teach all aspects of the Applicants invention, either explicitly or implicitly.

Domenighini fails to describe or demonstrate that an LT-A protein having both the amino acids at the position corresponding to Ser-63 of SEQ ID NO:7 and Arg-192 replaced with another amino acid that is immunogenic and detoxified as currently claimed. Furthermore, the allegation that Pizza et al. discloses that Arg-192Asn mutation “decreases the rate of proteolysis and activation *in vivo*” does not in any way disclose the claimed double mutants or indicate their toxicity.

Therefore, claim 1 and all claims dependent therefrom are not anticipated by Domenighini, and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

**35 U.S.C. § 103**

Claim 22 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Domenighini et al. (*supra*) in view of the reference of Clements et al. (U.S. Patent No. 6,019,982; hereinafter “Clements”). Claim 22 has been canceled; however, limitations of claim 22 have been incorporated into claim 1. Accordingly, this rejection will be addressed with respect to claim 1. Domenighini is cited for teaching DNA molecules that encode mutant detoxified heat labile toxin of *E. coli* and mutant detoxified cholera toxin having mutations in the A subunit at positions 63 and 192. The Office Action acknowledges that Domenighini fails to disclose an Arg192Gly mutation. Clements is cited for teaching the Arg192Gly mutation. The Office Action alleges:

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the mutation of Domenighini at position 192 from Asn to Gly as taught by Clements, because Clements and Domenighini et al. are both directed to the site directed mutagenesis of heat labile toxin of *E. coli* at position 192, and Clements et al. teach the advantage of substituting Gly at position 192 as yielding a stable, detoxified mutant that is devoid of ADP-ribosyl transferase activity, but retains its activity as an immunological adjuvant (see Clements, col. 8, lines 24-27 and 28-50). (Office Action, pages 8-9.)

The Office Action further alleges:

The person of ordinary skill in the art would have been motivated to substitute the amino acid for Gly at position 192 because the resultant protein/polypeptide would lack the potential to become toxic due to proteolytic activation, resulting in “no real or potential side-effects, such as diarrhea associated with its use (see col. 10, lines 5-14). (Office Action, page 9.)

Applicants respectfully traverse the rejection under 35 U.S.C. § 103 and the Office Action remarks and purported facts underlying the rejection on the following grounds.

The decision by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007) reaffirmed the viability of the four factual inquiries underlying an obviousness analysis provided in *Graham v. John Deere*, 148 USPQ 459, 467 (U.S. 1966). These factors include: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations. Moreover, the Supreme Court in *KSR* recognized that the “teaching, suggestion, or motivation” analysis provides a helpful insight in determining whether the claimed subject matter is obvious. This analysis is provided in MPEP 2142. In particular, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Both the teaching or suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art, not in applicant’s disclosure. See, e.g., *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Based on the foregoing, applicant respectfully submits the Office has failed to establish a *prima facie* case of obviousness.

The Office has failed to provide evidence that the claimed invention is a “predictable use of prior art elements according to their established functions.” *KSR*, page 13. In fact, the evidence is to the contrary. The cited art fails to provide evidence that a mutated CT-A or LT-A protein comprising the combined substitutions at the position corresponding to Ser-63 of SEQ ID NO:7 or SEQ ID NO:8 and the position corresponding to Arg-192 of SEQ ID NO:7 or SEQ ID NO:8 would not only retain immunogenicity, but also be detoxified and more resistant to trypsin proteolysis than wild type CT-A or LT-A.

The primary reference of Domenighini fails to disclose all of the elements of the pending claims, namely an immunogenic detoxified LT-A protein having amino acid substitutions at both Ser-63 and Arg-192. Moreover, Domenighini teaches away from the claimed subject matter in that the one and only mutant having a substitution at position

192 was an Arg192Asn mutant, which Domenighini believed had wild-type toxicity (see Table I at page 46).

In view of the perceived toxicity of the Arg192Asn mutant, Domenighini would not have been motivated to combine the Ser63Lys mutation with substitutions at position 192, as claimed. Therefore, Domenighini fails to provide any reasonable expectation of success that the combination of the two substitutions at Ser-63 and Arg-192 would produce a more stable, detoxified immunogenic LT-A protein.

Furthermore, Clements fails to teach or suggest that mutations should be made to more than one residue of LT-A. Clements fails to make mutations in other positions or suggest that multiple mutations would be desirable. In view of the clear teaching away by Domenighini and failure of Clements to teach multiple mutations, one of skill in the art would have had no reason to combine Clements and Domenighini to arrive at the claimed invention and a *prima facie* case of obviousness cannot be established or sustained.

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

**35 U.S.C. § 112, first paragraph, enablement**

Claims 1, 3, 4, 19, 23, and 25 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an enabling disclosure commensurate in scope with the claims. In particular, the Office Action alleges “the specification, while being enabling for immunogenic, detoxified proteins comprising the amino acid of subunit A of an *E. coli* heat labile toxin (LT-A) wherein the amino acids at positions Ser-63 and Arg-92 of SEQ ID NO:7 are replaced with another amino acid, and further wherein the amino acid at position Ser-63 is replaced with Lys-63 and the amino acid at position Arg-192 is replaced with Asn-192 or Gly-192, does not reasonably provide enablement for immunogenic, detoxified proteins comprising **any** amino acid replacement at Arg-192 as instantly claimed” (Office Action, pages 9-10). The Office Action cites Mikayama et al. (Proc. Natl. Acad. Sci. U.S.A. (1993) 90:10056-10060) in support of the position that “even a single amino acid difference may account for

markedly different biological activities" (Office Action, page 11). The Office Action further cites Rudinger et al. (Peptide Hormones Biol. Council (June, 1976), pages 5-7) for teaching that "amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study" (Office Action, pages 11-12). Applicants respectfully traverse the rejection.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants respectfully submit that the current claims indeed comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. The as-filed specification clearly teaches the claimed double mutants in which any amino acid residue is substituted for the specified Ser63 and Arg192.

Still further evidence is presented herewith. In particular, Ref. C1 of IDS attached hereto (Park et al. (1999) *Exp. & Mol. Medicine* 31(2):101-107) evidences that the properties of mutations to Ser63 other than those exemplified can be extrapolated to a certain degree. Park et al. shows that substituting Tyr for Ser also detoxified LT, thus showing that residue 63 can tolerate various mutations.

Furthermore, the trypsin cleavage site of LT was well-known at the time of filing, therefore, it is reasonable to expect that the properties of the exemplified Arg192 mutants are shared by other mutants which remove the trypsin recognition sequence. The present

disclosure lies in recognizing that mutations at these two positions give rise to a more stable and more immunogenic protein, not in the specific mutations at these positions.

Given the teachings of the specification and state of the art regarding LT specifically, it is clear that the references cited by the Office in no way establish unpredictability of the claimed subject matter. To the contrary, neither Mikayama nor Rudinger disclose anything about LT and, therefore, do not in any way negate the evidence of record regarding substitutions in LT proteins as claimed.

For all the foregoing reasons and the reasons of record, withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

**CONCLUSION**

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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Respectfully submitted,

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